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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/521,989 | 11/03/2005 | Hesson Chung | 4696-0110PUS1 | 1940 |

2292 7590 12/09/2009

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| EXAMINER | |
|---|---|
| PALENIK, JEFFREY T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1615 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 12/09/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/521,989 | CHUNG ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey T. Palenik | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,11,12,17-19,21-27,35,36,41-44 and 46-58* is/are pending in the application.

4a) Of the above claim(s) *1-7,11,12,17-19,21-25 and 48-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27,35,36,41-44,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Amendments and Remarks filed, filed 17 August 2009, in the matter of Application N° 10/521,989, in response to the Notice of Non-Responsiveness mailed by the Office on 15 July 2009. Said filings are entered on the record. The Examiner further acknowledges the following:

No claims have been added.

Claims 28-31 are newly cancelled.

Claims 26, 27, 35, 36, 41, 42 and 46 have been amended for clarity with support being lent from the original submission.

No new matter has been added.

Thus, claims 26, 27, 35, 36, 41-44, 46 and 47 now represent all claims currently under consideration.

### INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been filed for consideration.

### WITHDRAWN OBJECTIONS/REJECTIONS

Abstract of the Invention

Applicants' amendment to the Abstract of the Invention is sufficient enough to render the objection moot.

Rejections under 35 USC 112

Applicants' amendments to claims 26, 27 and 42 are sufficient enough to render moot the indefiniteness rejection under 35 USC 112, second paragraph. Thus, said rejection has been **withdrawn**.

Rejection under 35 USC 102(b)

Applicants' amendment to claim 26 alone is sufficient enough to overcome the rejection to claims 26, 27, 35, 36, 41-44, 46 and 47 under 35 USC §102(b) as being anticipated by Carrier et al. (WO 98/49848). Thus, said rejection stands **withdrawn**.

Rejection under 35 USC 102(e)

Applicants' Declaration filed under 37 CFR 1.132 on 2 March 2009 has been reviewed by the Examiner and is considered to be a sworn statement establishing the Chung reference as having the same inventive entity as the instant application, thereby rendering the Chung reference unavailable under 102(e). Thus, said rejection stands **withdrawn**.

Rejection under Double Patenting

Applicants' terminal disclaimer filed on 17 August 2009 was reviewed and approved on 20 August 2009. The terminal disclaimer has been recorded. The rejection of provisional non-statutory obviousness-type double patenting is hereby **withdrawn**.

US Application N° 10/521,695 has been abandoned thereby rendering moot the rejection under provisional non-statutory obviousness-type double patenting.

## MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Correspondence dated 12 August 2009 since either the grounds or art on which they were previously set forth continues to read on the amended limitations.

## CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-31, 35, 36, 41-44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woo et al. (WO 02/13815).

The instant claims are directed to a mucoadhesive formulation, as discussed above.

Woo et al. teach an oral composition comprising an insoluble drug, emulsifier (e.g. surfactant) and an oil (claims 1, 2 and 6). Claims 2 and 3 teach paclitaxel as the insoluble drug. Claim 7 teaches the following weight ratio ranges: 1-100 for the additive (e.g. co-surfactant), 5-100 for the emulsifier (e.g. surfactant), and 1-100 for the oil, all of which are based on 1 part by weight of the drug. Claim 8 teaches ethanol and/or polyethylene glycol as additives. Claim 9 teaches the emulsifier as comprising such compounds as polyoxyethylene-polyoxypropylene copolymer and monoglycerides. Claim 10 teaches the oil as comprising such compounds as squalene and squalane. Monoglycerides are taught in claims 9 and 10 as well as on pages 5 and 6, as other forms of emulsifiers and/or oils. The monoglyceride glyceryl monoleate is expressly taught in the formulation of Example 8. For example, a preferred monoglyceride prepared from oleic acid is taught (pg. 6, lines 18-19). Triglycerides are similarly taught as oil components in the form of fatty acid triglycerides such as fractionated coconut oil (pg. 6, lines 16-17). Formulation of the composition into a dissolved or liquid state such as a solution, emulsion or micro-emulsion, is the preferred route particularly since the liquid composition is taught as being used to fill hard and soft gelatin capsules (page 7, lines 14-21).

Neither the claimed percent ranges for components nor the 2-20 carbon atom triglyceride compounds, as instantly claimed are expressly taught by Woo et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising an insoluble drug, a monoglyceride, an oil, an

emulsifier and an additional additive, as suggested by Woo, modify the amounts and ratios of the ingredients, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Woo expressly teaches composition embodiments which comprise an insoluble drug such as paclitaxel, admixed with emulsifiers, oils and additives. Triglycerides, while not being taught as expressly as the other claimed ingredients of the composition, are taught as components used as or in combination with the emulsifiers (e.g. surfactants) and/or the oils (pg. 5 and 6). While the reference does not expressly teach ranges, as claimed by Applicants, the values and formats of each parameter with respect to the claimed composition are adjustable. It thus follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. In the instant case, it would have been within the purview of the skilled artisan to adjust the amount and type of monoglyceride and/or triglyceride compounds used in the composition. Thus, it would have been customary for an artisan of ordinary skill, to adjust percent ranges of the components in the composition, in order to achieve the desired mucoadhesive formulation. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

## RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 26, 27, 35, 36, 41-44, 46 and 47 under 35 USC 103(a) as being unpatentable over the teachings of Woo et al. have been fully considered but they are not persuasive.

Applicants assert that the claimed composition is "totally different" from that which is taught by the Woo reference in terms of the mechanism for increasing oral bioavailability of the active agent. Applicants more specifically argue that Woo adds a verapamil derivative for inhibiting *p*-glycoprotein, a protein which inhibits the absorption o the insoluble drugs. Applicants asset that the addition of such *p*-glycoproteins as taught in the Woo reference "makes it possible to cause drug-drug interactions", as evidenced by the Kruijtzer journal article (provided by Applicants).

In response, the Examiner respectfully disagrees and maintains that no such interactions have been proven by Applicants to occur. Review of the highlighted passage of the Kruijtzer journal article reveals a concern that there may be *potential* interactions between combinations of paclitaxel and Cyclosporin A with other medications which are also substrates of the same drug transporter (i.e. substrates of Cyclosporin A). At no time does the article discuss the combination of paclitaxel with verapamil or any of its derivatives. Comparison of the chemical structures of both Cyclosporin A and verapamil (e.g. Wikipedia) reveals that the two are nowhere near to being structurally homologous. Furthermore, that Applicants' invention "comprises" the instantly claimed components, does not preclude the inclusion of other compounds such as a *p*-glycoprotein. Given that the Woo reference is directed to a composition comprising an insoluble drug such as paclitaxel and a verapamil derivative which does not cause

any adverse effects (Abstract; claims 1-3), it follows that the invention continues to read on the instantly claimed invention.

Applicants also traverse the teaching of a monoolein in the Woo reference stating that the reference "fails to disclose or suggest combined use of monoolein with specific oil and any example or experimental data covering any favorable effects".

Regarding these remarks, Applicants are respectfully reminded that the Office does not have the facilities for examining and comparing Applicants' composition to those which are taught in the art (e.g. Woo et al.) in order to establish that the prior art either does not possess the same material structural and functional characteristics of the claimed composition or even that it departs from the instantly claimed invention (i.e. comparison on the basis of mechanisms for increasing drug bioavailability). In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed methods/products are functionally different than those taught by the prior art and to establish patentable differences (e.g. experimental data demonstrating any alleged favorable effects). See *Ex parte Phillips*, 28 USPQ2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

Claims 26-31, 35, 36, 41-44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carrier et al. (WO 99/49848).

The instant claims are directed to a mucoadhesive formulation, as discussed above.

The teachings to Carrier et al., discussed above [*are reproduced below for Applicants' convenience*].

*Carrier et al. teach an orally administrable pharmaceutical composition comprising an* ***anticancer drug*** *as an active ingredient dissolved in a carrier system comprising at least one hydrophobic component and at least one surfactant (claims 1 and 17). Example 5 teaches a specific embodiment comprising* ***paclitaxel*** *(1.4% by weight), the* ***emulsifier Tween 80*** *(43% by weight), the* ***caprylic/capric triglyceride*** *Miglyol 812 as the oil (28.7% by weight), and* ***soybean oil as a monoglyceride semi-synthesized from triglycerides of vegetable oil*** *(3.6% by weight). Example 5 also teaches the presence of additives such as linoleic acid (3.4% by weight) as well as ethanol (6.1% by weight). All compositions of the Examples to Carrier et al. are taught as resulting in a liquid or semi-solid pre-concentrate formulation (page 7, lines 22-23).*

Carrier does not expressly teach in the claims or Examples the use of specific types of triglycerides (i.e. vegetable oils) or the specific percent amount of alcohol or polyol additive within the composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising an insoluble drug, a monoglyceride, an oil, an emulsifier and an additional additive, as suggested by Carrier, modify the amounts and ratios of the ingredients, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Carrier teaches that the compound used as an oil in Example 5, namely Miglyol 812, is functionally equivalent to many other hydrophobic compounds such as vegetable oils (e.g. olive, corn and soybean). Similarly, Example 5 teaches the prepared composition as containing 6.1% of the

additive ethanol; just outside of the instantly claimed range for the additive. One with ordinary skill in the art would substitute and/or vary the levels of these materials, within the ranges taught by Carrier, during the process of routine experimentation in order to optimize the fluidity and stability of the composition.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

## RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 26, 27, 35, 36, 41-44, 46 and 47 under 35 USC 103(a) as being unpatentable over the teachings of Carrier et al. have been fully considered but they are not persuasive.

Applicants allege that the Carrier reference is silent to any support regarding the composition comprising a monoolein. Applicants further attest that the composition which is taught does not contain the instantly claimed 0.01-20 wt% of insoluble drug. Applicants assert that the Carrier reference necessarily includes hydrophilic components which would impede the bioavailability of the insoluble drug. Lastly, Applicants argue that the reference fails to teach, suggest or provide any supportive data regarding the combined use of monoolein with specific oil and its advantages.

Regarding the aforementioned first and last arguments, the Examiner respectfully submits that the reference does teach and suggest the use of monoolein compounds. PEG-6 glyceryl

mono oleate (Labarafil M 1944 CS) is taught as being a functional equivalent to Labrasol ( both are PEG glyceryl fatty acid esters; see pg. 4, lines 29-32). Labrasol is used throughout the Examples discussed above. Given their functional equivalence, it follows, absent a showing of evidence to the contrary, that the ordinarily skilled artisan would be motivated to substitute one for the other.

Regarding Applicants' remarks concerning the amount of insoluble drug, the Examiner respectfully disagrees and maintains that the limitation is met, for example, by the Examples. Example 5 teaches the use of 68 micrograms (e.g. 0.068g) of paclitaxel in a formulation totaling five grams. This calculates to approximately 1.4 wt%.

Lastly, regarding the hydrophilic component, the Examiner again respectfully disagrees with Applicants' position and submits that the hydrophilic component is taught by the reference as being an *optional* component (see e.g. pg. 4, lines 16-18) [*emphasis added*].

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

All claims under consideration remain rejected; no claims are allowed.

## CONCLUSION

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615